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SCIENCE MEDICINES HEALTH

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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Epidyolex

cannabidiol

Procedure no: EMEA/H/C/004675/P46/005 - EMEA/H/C/004675/P46/006

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Submission of information about paediatric studies completed after 26 January 2007 in accordance with Article 46 of Regulation 1901/2006, as amended. GW Research Ltd (GW) is submitting the following paediatric studies, which completed on October 2 2018:

Study 1
Protocol No. GWEP1447 (Double-blind Phase)
A Phase 2, Double-blind, Randomized, Placebo-controlled, Pharmacokinetic Trial in Two Parallel Groups to Investigate Possible Drug-drug Interactions Between Stiripentol or Valproate and GWP42003-P in Patients with Epilepsy

Patients who completed Study 1 were invited to enter Study 2.

Study 2
Protocol No. GWEP1447 (Open-label Extension)
A Phase 2, Double-blind, Randomized, Placebo-controlled, Pharmacokinetic Trial in Two Parallel Groups to Investigate Possible Drug-drug Interactions Between Stiripentol or Valproate and GWP42003-P in Patients with Epilepsy

1.1. Steps taken for the assessment

Submission date:	16 March 2020
Start of procedure:	30 March 2020
Rapporteur's preliminary assessment report circulated on:	13 May 2020
Rapporteur's updated assessment report circulated on:	20 May 2020
Rapporteur's response assessment report circulated on:	3 July 2020
Updated report circulated	16 July 2020
CHMP adoption of conclusions:	23 July 2020

1.2. Introduction

Epidyolex (sponsor product code GWP42003-P) was approved, via the EU centralised procedure by the Committee for Medicinal Products for Human Use (CHMP), with European Commission (EC) decision

issued on 19th September 2019 for the following indication: Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.

The objective of this study was to determine whether GWP42003-P affects the pharmacokinetic (PK) profile of stiripentol (STP) or valproate (VPA). And secondary:
To assess the safety and tolerability of GWP42003-P in the presence of STP or VPA.
To assess whether GWP42003-P affects the PK profile of: 2 propyl-4-pentenoic acid (4-ene-VPA), Clobazam (CLB), N-desmethylclobazam (N-CLB), Levetiracetam (LEV), Topiramate (TPM) in patients also being treated with STP or VPA and other antiepileptic drugs (AEDs).

The Applicant intends to submit a grouped type 2 variation under the classification C.I.5, along with 3 other drug-drug interaction studies that will have impact on the SmPC, planned for Q2 2020. However, as GWEP1447 falls under Article 46, the study report is being provided now for information. The grouped Type II variation for the 4 drug-drug interaction studies (including GWEP1447) has been agreed with the EMA PM and the related communication is enclosed with the cover letter.
The GWEP1447 study results further support the approved Epidyolex SmPC (section 4.5) statement on the Epidyolex-Stiripentol interaction. The Applicant will also propose the following highlighted updates to be included in section 4.5 as a result of GWEP1447:

Stiripentol

When cannabidiol was combined with stiripentol in a healthy volunteer trial there was an ~~minor~~ increase in stiripentol levels of 28% for maximum measured plasma concentration (Cmax) and 55% for AUC. In patients, however, the effect was smaller, with an increase in stiripentol levels of 17% in C_{max} and 30% in AUC. The clinical importance of these results, has not been studied. The patient should be closely monitored for adverse drug reactions."

CHMP comments

The MAH has not submitted a full clinical study report (CSR) but merely a synoptic CSR. Additional data are presented as summary tables for baseline characteristics, demographics, and safety data and as patient narratives for Serious Treatment-emergent Adverse Events and Other Significant Events. The text as proposed is not endorsed in this procedure, but will await the planned type 2 variation.
A revised text is proposed to replace the text given by the Applicant for section 4.5.

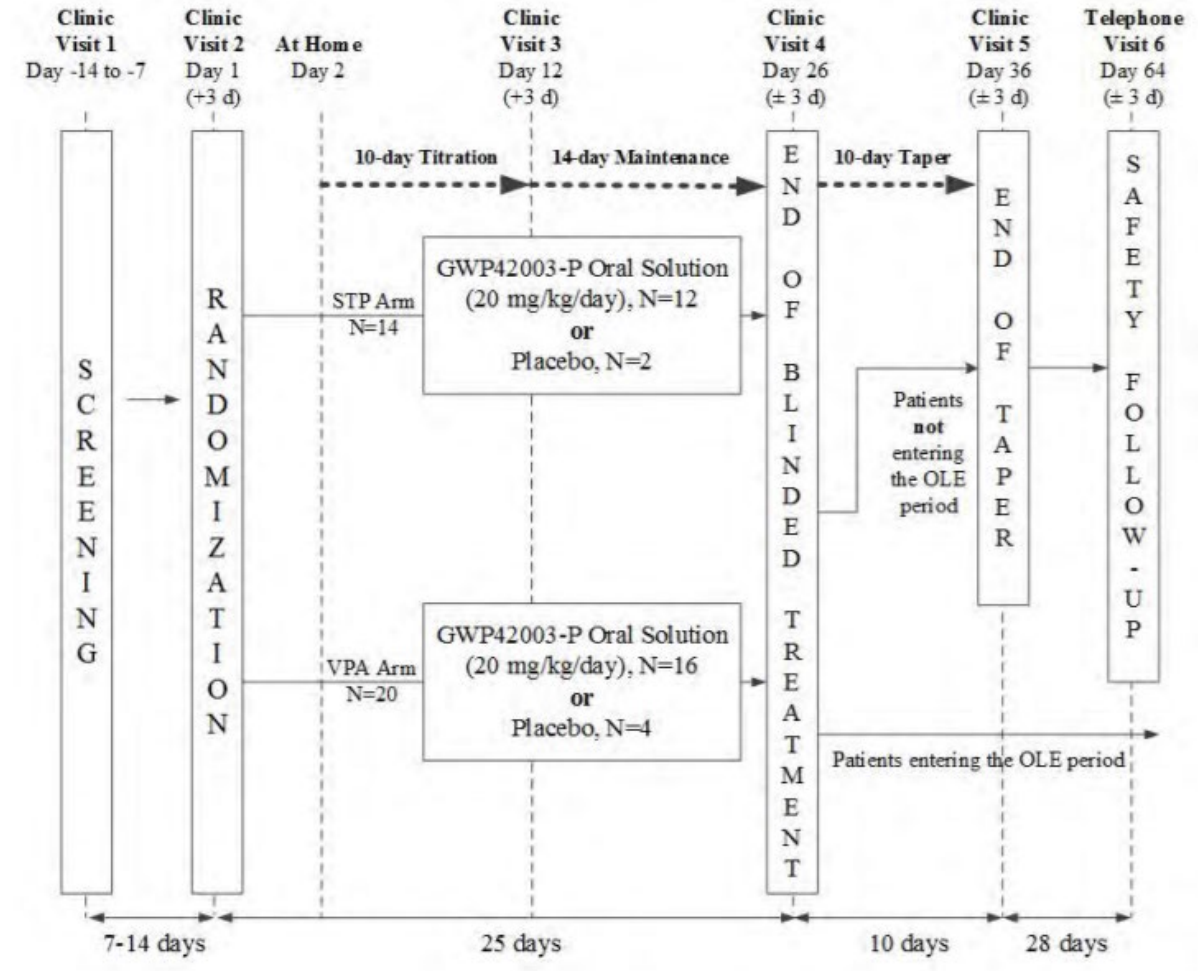
2. Summary of data submitted

2.1. Methodology

2.1.2 Study design

Study 1 was a phase 2, multisite, double-blind (DB), randomized, placebo-controlled, PK trial in 34 patients on stable STP or VPA treatment. Eligible patients entered the trial at Visit 1 (Day -14 to Day -7) and began a 7- to 14-day baseline period. Patients who satisfied all eligibility criteria were then randomized at Visit 2 (Day 1) to receive GWP42003-P or placebo via STP or VPA arms in a 4:1 ratio. Patients received their first dose of GWP42003-P/placebo at home on Day 2. Patients titrated GWP42003-P or placebo to a maintenance dose or equivalent maintenance dose level (20 mg/kg/day GWP42003-P or equivalent volume of placebo) over 10 days and remained at this dose for 14 days (Day 12 to Day 25). A further clinic visit occurred on Day 12 (Visit 3), and patients returned to the clinic for an end-of-treatment visit after 25 days of treatment (Visit 4, Day 26) or earlier if they withdrew prematurely. Upon completion of the blinded period of the trial (Day 26), patients were invited to receive GWP42003-P during the open-label extension (OLE) period. If a patient chose not to enter the OLE period, and/or the investigator did not feel it was in their best interests, patients then tapered down GWP42003-P or placebo during a 10-day taper period and returned to the clinic for an end-of-taper period visit (Visit 5, Day 36) followed by a safety follow-up visit 28 days later (Visit 6, Day 64). All patients were taking either STP or VPA, with or without other concomitant AEDs. Pharmacokinetic samples were taken on Day 1 (Visit 2), before commencing treatment with GWP42003-P or placebo (investigational medicinal product [IMP]), and after completing 25 days of treatment (Day 26, Visit 4) with IMP.

Figure 5.1-1 Trial Schema



OLE, Open-label extension; STP, Stiripentol; VPA, Valproic acid.

[redacted]

CHMP comments

This trial used a randomized, DB design and a placebo concurrent control, as recommended by the European Medicines Agency (EMA) Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders. The treatment periods (including the titration periods), 10 day taper period, and 28 day follow-up period were chosen based on revised guidance from the EMA on the conduct and design of drug-drug - interaction studies. This is endorsed.

2.1.3 Number of Patients (Planned and Analyzed):

A total of 34 patients were planned for randomization (14 patients in the STP and 20 patients in the VPA arm); a total of 35 patients were randomized and 34 patients received 20 mg/kg/day GWP42003-P or placebo.

CHMP comments

A total of 34 patients (14 patients in the STP and 20 patients in the VPA arm) were planned for randomization. No power calculation is presented. The statistical significance of findings may be less relevant than the clinical interpretations of the findings. The study is expected to be adequate in sample size for a clinical conclusion.

2.1.4 Diagnosis and Main Criteria for Inclusion:

Patients were to be male or female aged between 16 and 55 years old (inclusive) (18 to 55 years in Sweden) and had to be taking STP or VPA and no more than 2 other AEDs during the blinded period of the trial (in VPA arm only, patients must not have been receiving STP). All AEDs or interventions (including vagus nerve stimulation and/or ketogenic diet) must have been stable for 4 weeks prior to baseline and remained stable throughout the blinded phase of the trial. Patients had to have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition. Patients must have experienced at least 1 countable uncontrolled seizure of any type (i.e., tonic-clonic, tonic, clonic, atonic, partial onset or focal; focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness, focal seizures evolving to bilateral secondary generalization) within 2 months prior to randomization. Patients and/or their legal representatives were willing and able to give informed consent/assent, and patients were willing and able (in the investigator's opinion) to comply with all trial requirements.

2.1.5 Investigational Medicinal Product, Dose and Mode of Administration, Batch Number:

GWP42003-P was presented as a clear, colorless to yellow solution containing 100 mg/mL cannabidiol (CBD) in the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose) and strawberry flavouring . GWP42003-P was taken orally as per intended commercial therapeutic use and was to be taken twice daily (b.i.d.) (morning and evening) immediately after the patients' usual STP or VPA administration, following the dosing schedule below: • Day 2, patients commenced titration with GWP42003-P at home to a maintenance dose of 20 mg/kg/day over a period of 10 days (Day 2 to Day 11). • After titration with GWP42003-P, patients continued to take this maintenance dose of GWP42003-P/placebo for 14 days (Days 12 to 25), before coming in for the final PK visit on Day 26. • On Day 27, patients either entered a tapering period (10% per day over 10 days) or, if the patient elected to participate in the OLE, they entered a 10-day period of simultaneous tapering (of GWP42003-P/placebo) and titration (of GWP42003-P) in order to maintain blinding. Patients used their own supply of STP or VPA. STP or VPA was taken orally as prescribed.

CHMP comments

The exact timing in relation to food intake was not recorded, but administration is expected to be in some relation to a meal as CBD was to be taken in the morning and in the evening. Exposure of CBD is overall consistent with exposure previously seen when administered with food.

2.1.6 Comparator, Dose, and Mode of Administration; Batch Number:

GW supplied the placebo, which was an oral solution matched to GWP42003-P, containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. Placebo was taken orally b.i.d. (morning and evening) immediately after the patients' usual STP or VPA administration, and followed the same dosing schedule described for GWP42003-P.

2.1.7 Duration of Treatment:

The screening period was 8 days (Day -14 to Day -7). The DB treatment period was 25 days (10-day titration period and 15-day maintenance period).

2.1.8 Criteria for Evaluation:

Efficacy: Not applicable.

Pharmacokinetics/Pharmacodynamics/Pharmacogenetics:

The primary endpoints of the trial were the dose-normalized (DN) PK parameters (maximum measured plasma concentration [Cmax], time to maximum plasma concentration [tmax], area under the plasma concentration-time curve over a dosing interval, where tau is the dosing interval [AUCtau], and area under the concentration-time curve from time zero to last observable concentration at time t [AUC0-t]) for the following analytes when STP or VPA was taken alone or in combination with GWP42003-P or placebo:

- STP
- VPA
- CBD

The secondary endpoints of the trial were the safety parameters and the DN PK parameters

Cmax, tmax, AUCtau, and AUC0–t for the following analytes:

- 4-ene-VPA
- CLB
- N-CLB
- LEV

• TPM

Cytochrome P450 (CYP), CYP2C19, and CYP3A4 patient genotype analyses were performed.

Safety:

The safety and tolerability of GWP42003-P compared with placebo when taken in combination

with STP or VPA were assessed using the following parameters:

• Adverse events (AEs)

• 12-lead electrocardiogram (ECG)

• Clinical laboratory parameters (biochemistry, hematology and urinalysis)

• Physical examination.

• Vital signs

• Columbia-Suicide Severity Rating Scale

• Seizure frequency

• Abuse liability

CHMP comments

The MAH has clearly presented the primary and secondary endpoint of each part of the studies (double blind phase and open-label extension). All the chosen endpoints are considered relevant or the corresponding objectives.

2.1.9 Pharmacokinetic /Pharmacogenetic Methods:

Bioanalytical: Validated liquid chromatographic-tandem mass spectrometry bioanalytical methods were used to quantify concentrations of CBD, STP, VPA, 4-ene-VPA, CLB, N-CLB, LEV, and TPM in human plasma. Pharmacokinetics: The plasma concentration/time curves of STP, VPA, 4-ene-VPA, CLB, N-CLB, LEV, and TPM) were assessed at Day 1 (Visit 2) and STP, VPA, 4-ene-VPA, CLB, N-CLB, LEV, TPM, and CBD at Day 26 (Visit 4). Patients were given their daily dose of STP or VPA at a scheduled time during Visit 2 and Visit 4 and GWP42003-P/placebo immediately afterward (at Visit 4 only) to facilitate the accurate timing of blood samples required for PK analysis. Blood samples were taken by either direct venipuncture or an indwelling cannula inserted into a forearm vein at the following time points: predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, and 12 hours postdose. The timing of each PK sample was relative to the morning dose of STP or VPA. The predose blood sample was taken within 30 minutes prior to dosing. The allowable window for postdose blood sample collection was ± 2 minutes up to and including 1 hour postdose, ± 5 minutes from 1.5 hours up to and including 6 hours postdose, and ± 1 hour at 12 hours postdose.

In the event of an AE that, in the opinion of the investigator, was related to a concomitant AED, additional blood samples may have been collected. Analyses of all PK samples for a given analyte were conducted at a single bioanalytical laboratory. Sample volume requirements and processing procedures were detailed in a separate laboratory manual. Pharmacogenetics: Genetic testing was conducted, if specific consent was obtained from the patient, to look at sequencing CYP isoforms, with particular focus on CYP2C19 and CYP3A4, involved in the metabolism of AEDs and CBD. No PK/pharmacogenetic correlations were planned in this trial.

CHMP comments

Overall, the bioanalytical methods applied for the determination of CBD, STP, VPA, CLB, N-CLB. LEV and TPM concentrations in human serum are considered acceptable.

Genetic testing was conducted, if specific consent was obtained from the patient, to look at sequencing CYP isoforms, with particular focus on CYP2C19 and CYP3A4, involved in the metabolism of AEDs and CBD. No PK/pharmacogenetic correlations were planned in this trial. This is accepted.

2.1.10 Statistical Methods:

All statistical testing was performed in accordance with standard practice. There were no predetermined covariates and no plans to replace missing data points. There was no formal sample size calculation, and analyses were descriptive only. Plasma concentrations of STP, VPA, 4-ene-VPA, CBD, and AEDs were displayed graphically (geometric mean concentrations by treatment group and visit), summarized (by nominal time point and visit), and listed for the PK population. PK parameters (Cmax and AUCtau) were calculated by noncompartmental analysis, listed by patient, and summarized by treatment group and visit. For statistical analysis of a drug-drug interaction (DDI) between GWP42003-P and STP or VPA, a standard 90% confidence interval (CI) approach for the between time point ratios of geometric means of Cmax and AUCtau was carried out on logarithmic scale using a linear mixed effect model. The no-effect boundary was set between 0.5 and 2.0, and if the 90% CI for the ratio of the geometric means of a PK variable fell within the interval [0.5, 2.0], a lack of meaningful effect was declared. Estimates were back transformed to provide summaries on the original scale. The model included a fixed effect term for the PK assessment period. An unstructured covariance matrix was used. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects. Plasma concentrations and PK parameters for VPA, STP, LEV, and TPM were summarized descriptively for the PK population. However, any DDI was not formally assessed. Safety data were analysed descriptively; summaries and listings were generated for the safety population set and presented by treatment.

CHMP comments

There was no formal sample size calculation, and analyses were descriptive only.

2.2. Results

2.2.1 Summary of Results Disposition, Demographics, and Baseline Characteristics:

In total, 35 patients were screened for participation and randomized. Among the 14 patients in the STP arm (Table 8.2.1-1), 2 were randomized to placebo and 12 were randomized to GWP42003-P. Among the 21 patients in the VPA arm (Table 8.2.2-1), 4 were randomized to placebo and 17 were randomized to GWP42003-P; 1 patient randomized to GWP42003-P withdrew before receiving treatment. All patients were White. The mean age in the STP arm was 29.86 years, and the mean body mass index (BMI) was 26.49 kg/m2. The mean age in the VPA arm was 29.27 years, and the mean BMI was 27.02 kg/m2 . All patients had a history of seizures at baseline and the most commonly occurring seizure type in both treatment arms was complex partial seizures (50.0% in the STP arm and 55.0% in the VPA arm). All but 1 patient in the STP arm were taking other AEDs in addition to STP or VPA at baseline.

Table 8.2.1-1 Summary of Demographics – STP Arm (Safety Population)

Parameter Statistic	Placebo (N=2)	GWP42003-P (N=12)	Total (N=14)
Age (years)			
Mean (SD)	20.95 (3.04)	31.34 (11.09)	29.86 (10.91)
Median (min, max)	20.95 (18.8, 23.1)	29.35 (18.0, 53.8)	28.20 (18.0, 53.8)
Sex			
Male n (%)	2 (100.0)	7 (58.3)	9 (64.3)
Female n (%)	0	5 (41.7)	5 (35.7)
Race			
White n (%)	2 (100.0)	12 (100.0)	14 (100.0)
Weight (kg)			
Mean (SD)	85.50 (12.02)	81.50 (22.17)	82.07 (20.72)
Median (min, max)	85.50 (77.0, 94.0)	82.50 (53.0, 124.0)	82.50 (53.0, 124.0)
Body mass index (kg/m^2)			
Mean (SD)	25.92 (4.84)	26.58 (5.53)	26.49 (5.26)
Median (min, max)	25.92 (22.5, 29.3)	26.01 (17.4, 36.9)	26.01 (17.4, 36.9)

max, Maximum; min, Minimum; SD, Standard deviation.

[redacted]

Table 8.2.2-1 Summary of Demographics – VPA Arm (Safety Population)			
Parameter Statistic	**Placebo (N=4)**	**GWP42003-P (N=16)**	**Total (N=20)**
Age (years)			
Mean (SD)	29.80 (6.60)	29.14 (11.40)	29.27 (10.47)
Median (min, max)	29.80 (23.7, 35.9)	25.95 (17.4, 54.5)	25.95 (17.4, 54.5)
Sex			
Male n (%)	3 (75.0)	10 (62.5)	13 (65.0)
Female n (%)	1 (25.0)	6 (37.5)	7 (35.0)
Race			
White n (%)	4 (100.0)	16 (100.0)	20 (100.0)
Weight (kg)			
Mean (SD)	86.25 (22.63)	82.25 (23.00)	83.05 (22.39)
Median (min, max)	85.00 (60.0, 115.0)	81.00 (51.0, 148.0)	82.00 (51.0, 148.0)
Body mass index (kg/m^2)			
Mean (SD)	27.56 (6.14)	26.89 (5.53)	27.02 (5.49)
Median (min, max)	28.46 (19.4, 34.0)	25.17 (20.7, 39.7)	25.74 (19.4, 39.7)

[redacted]

CHMP comments

Demographic data has been presented adequately. The groups appear to be comparable except in regards of sex. Only Caucasians have been included, and all patients had a history of seizures at baseline and the most commonly occurring seizure type in both treatment arms was complex partial seizures (50.0% in the STP arm and 55.0% in the VPA arm). All but 1 patient in the STP arm were taking other AEDs in addition to STP or VPA at baseline. The presented interaction study has only been performed in patients between 16 and 55 years of age, but is considered relevant for other age groups except very young children < 1 year**.**

The minimum age of included patients is 17.4 years. No specific information regarding PK, efficacy or safety can be concluded from this study.

2.2.2 Pharmacokinetic results

Pharmacokinetic Profile – STP Arm

Geometric mean PK parameters for STP are summarized in Table 8.4.2.5.1.1-1

Table 8.4.2.5.1.1-1 PK Parameters for STP (STP Arm) (PK Population)					
Parameter PK Parameter	Visit Day	Placebo		GWP42003-P	
		n	Geometric Mean (CV%)	n	Geometric Mean (CV%)
t_{max} (h)[a]	1	2	3.94 (2.00, 5.88)	11	1.53 (0.25, 6.08)
	26	2	1.70 (1.40, 2.00)	9	2.07 (1.42, 6.03)
DN C_{max} (ng/mL/mg)	1	2	7.74 (16.3)	11	7.6 (80.0)
	26	2	7.65 (18.4)	9	10.7 (59.4)[c]
DN AUC_{tau} (ng·h/mL/mg)	1	2	49.7 (22.0)	11	52.3 (108.5)
	26	2	51.8 (41.3)	9	80.7 (66.8)

[a] Median (min, max).

[redacted]

On Day 26, CBD DN Cmax was 35.1 ng/mL/(mg/kg) (CV%: 64.4) and DN AUCtau was 203 ng·h/mL/(mg/kg) (CV%: 48.1); these parameters were consistent with previous trials (Table 8.4.2.5.1.2-1)

Table 8.4.2.5.1.2-1 PK Parameters for CBD on Day 26 (STP Arm) (PK Population)			
Parameter PK Parameter	Visit Day	GWP42003-P	
		n	Geometric mean (CV%)
t_{max} (h)[a]	26	10	4.05 (0.00, 6.02)
DN C_{max} (ng/mL/[mg/kg])	26	10	35.1 (64.4)
DN AUC_{tau} (ng·h/mL/[mg/kg])	26	10	203 (48.1)

[a] Median (min, max).

[redacted]

Geometric mean PK parameters for other AEDs and metabolites are summarized in Table 8.4.2.5.1.3-1

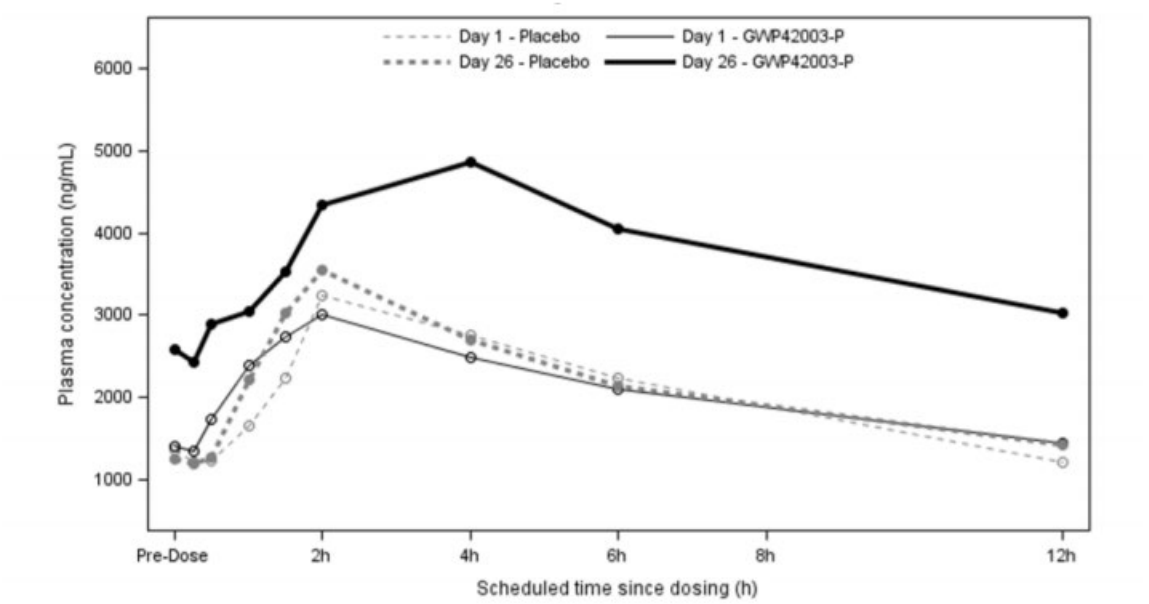
Table 8.4.2.5.1.3-1 PK Parameters for Other AEDs (STP Arm) (PK Population)					
Analyte **PK Parameter**	**Visit Day**	**Placebo**		**GWP42003-P**	
		n	**Geometric mean (CV%)**	**n**	**Geometric mean (CV%)**
VPA					
t_{max} (h)[a]	1	0	-	5	0.00 (0.00, 4.03)
	26	0	-	4	3.93 (0.00, 6.05)
DN C_{max} (ng/mL/mg)	1	0	-	5	184 (51.0)
	26	0	-	4	177 (48.6)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	5	1840 (44.1)
	26	0	-	4	1730 (44.7)
4-ene-VPA					
t_{max} (h)[a]	1	0	-	3	0.50 (0.25, 4.03)
	26	0	-	2	3.67 (1.50, 5.83)
DN C_{max} (ng/mL/mg)	1	0	-	3	0.144 (27.0)
	26	0	-	2	0.129 (36.4)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	3	1.34 (21.0)
	26	0	-	2	1.23 (40.4)
4-ene-VPA/VPA ratio					
DN C_{max} (ng/mL/mg)	1	0	-	3	0.000696 (29.1)
	26	0	-	2	0.000554 (49.0)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	3	0.00067 (30.6)
	26	0	-	2	0.000545 (38.3)
CLB					
t_{max} (h)[a]	1	0	-	4	5.06 (1.52, 11.02)
	26	0	-	3	6.03 (2.07, 10.97)
DN C_{max} (ng/mL/mg)	1	0	-	4	61.5 (33.3)
	26	0	-	3	73.4 (42.6)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	4	567 (38.1)
	26	0	-	3	692 (42.4)
N-CLB					
t_{max} (h)[a]	1	0	-	4	5.03 (0.00, 6.08)
	26	0	-	3	2.00 (0.53, 10.90)
DN C_{max} (ng/mL/mg)	1	0	-	4	508 (66.1)
	26	0	-	3	790 (36.7)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	4	5100 (63.5)
	26	0	-	3	7710 (35.5)

Table 8.4.2.5.1.3-1 PK Parameters for Other AEDs (STP Arm) (PK Population)					
Analyte PK Parameter	Visit Day	Placebo		GWP42003-P	
		n	Geometric mean (CV%)	n	Geometric mean (CV%)
N-CLB/CLB ratio					
DN C_{max} (ng/mL/mg)	1	0	-	4	8.26 (37.1)
	26	0	-	3	10.8 (34.1)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	4	9 (31.6)
	26	0	-	3	11.1 (33.6)
LEV					
t_{max} (h)[a]	1	1	1.00 (1.00, 1.00)	0	-
	26	1	1.00 (1.00, 1.00)	0	-
DN C_{max} (ng/mL/mg)	1	1	31.6	0	-
	26	1	38.9	0	-
DN AUC_{tau} (ng·h/mL/mg)	1	1	222	0	-
	26	0	-	0	-
TPM					
t_{max} (h)[a]	1	0	-	2	3.04 (2.08, 4.00)
	26	0	-	2	2.03 (2.00, 2.07)
DN C_{max} (ng/mL/mg)	1	0	-	2	65.1 (34.0)
	26	0		2	60.7 (35.2)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	2	658 (29.9)
	26	0	-	2	597 (27.6)

STP Plasma Concentrations

At all time points on Day 26, geometric mean plasma concentrations of STP in the presence of GWP42003-P were higher than on Day 1 (without GWP42003-P). By contrast, there was no clear difference between the STP plasma concentration vs. time curves between placebo groups on Day 26 compared with Day 1. The STP plasma concentration vs. time curves in the placebo group on Day 1 and Day 26 were also similar to that for Day 1 for the GWP42003-P group.

Figure 8.4.2.3.1-1 Geometric Mean Plasma STP Concentration Versus Time on Day 1 and Day 26 (STP Arm) (PK Population)



Day 1: Placebo, N=2; GWP42003-P, N=11.
Day 26: Placebo, N=2; GWP42003-P, N=9.

[redacted]

CHMP comments

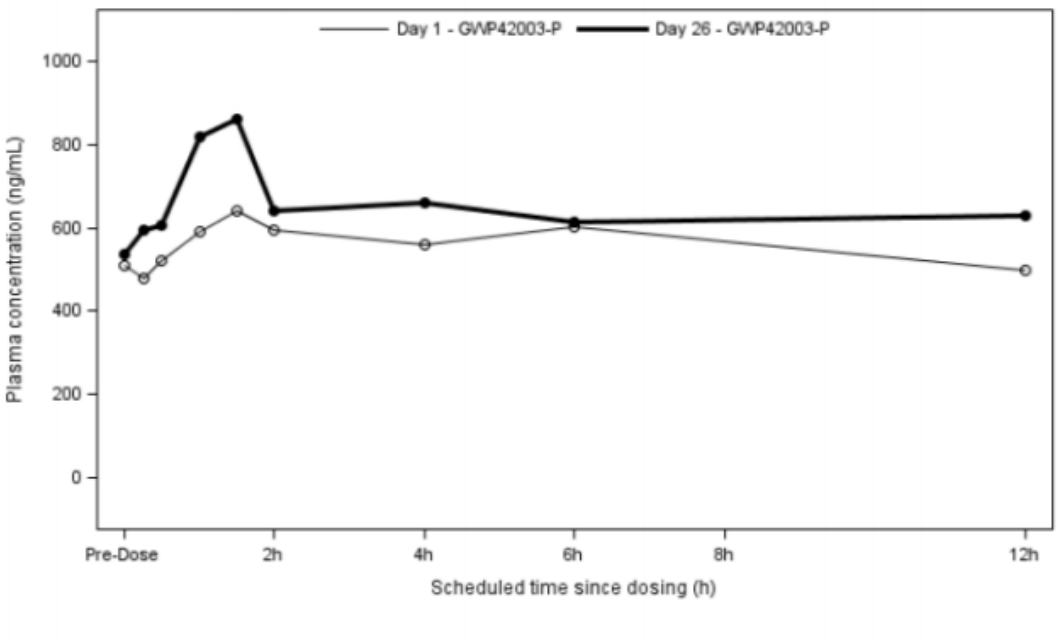
STP plasma concentrations increased significantly when co-administered with CBD, confirming a pharmacokinetic D-D interaction. Therefore, close monitoring of the patient should be performed when the two drugs are administered simultaneously. This information is adequately displayed in the SmPC**.**

Clobazam and N-Desmethylclobazam Plasma Concentrations

Clobazam plasma concentrations

On Day 26, plasma concentrations of CLB in the presence of GWP42003-P were higher than on Day 1 (without GWP42003-P) at early time points. After 2 hours, the plasma concentration profiles of CLB on Day 1 and Day 26 were generally similar (Figure 8.4.2.3.3.2-1, below).

Figure 8.4.2.3.3.2-1 Geometric Mean Plasma CLB Concentration Versus Time at Day 1 and Day 26 (STP Arm) (PK Population)



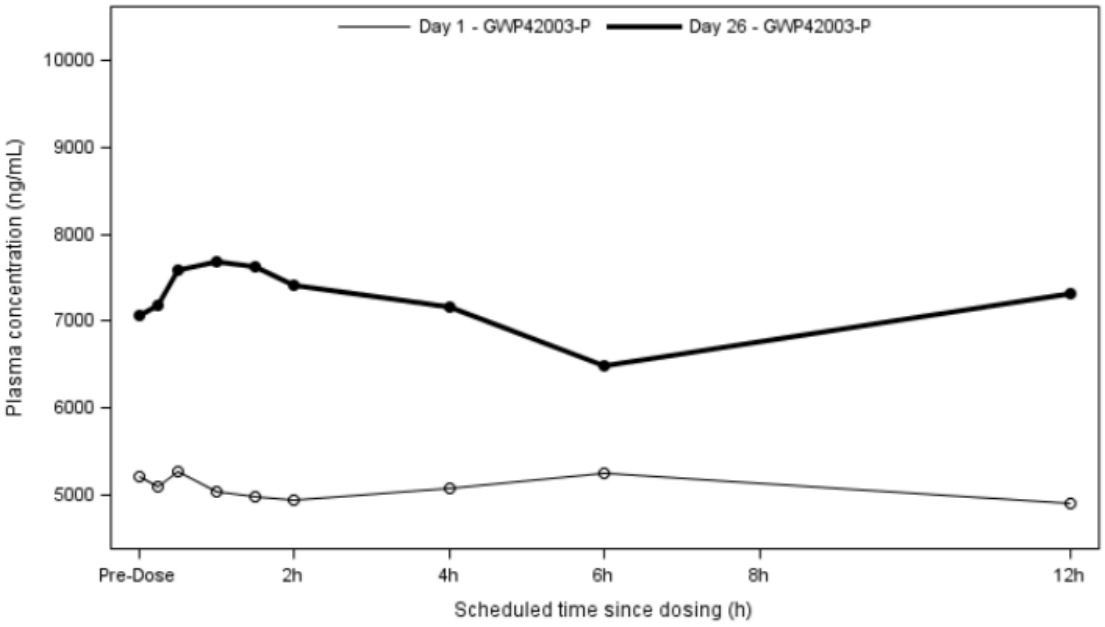
Day 1: Placebo, N=0; GWP42003-P, N=4.
Day 26: Placebo, N=0; GWP42003-P, N=3.

[redacted]

Clobazam and N-Desmethylclobazam Plasma Concentrations

On Day 26, plasma concentrations of N-CLB in the presence of GWP42003-P were higher than on Day 1 (without GWP42003-P) at all time points.

Figure 8.4.2.3.3.2-2 Geometric Mean Plasma N-CLB Concentration Versus Time at Day 1 and Day 26 (STP Arm) (PK Population)



Day 1: Placebo, N=0; GWP42003-P, N=4.
Day 26: Placebo, N=0; GWP42003-P, N=3.

[redacted]

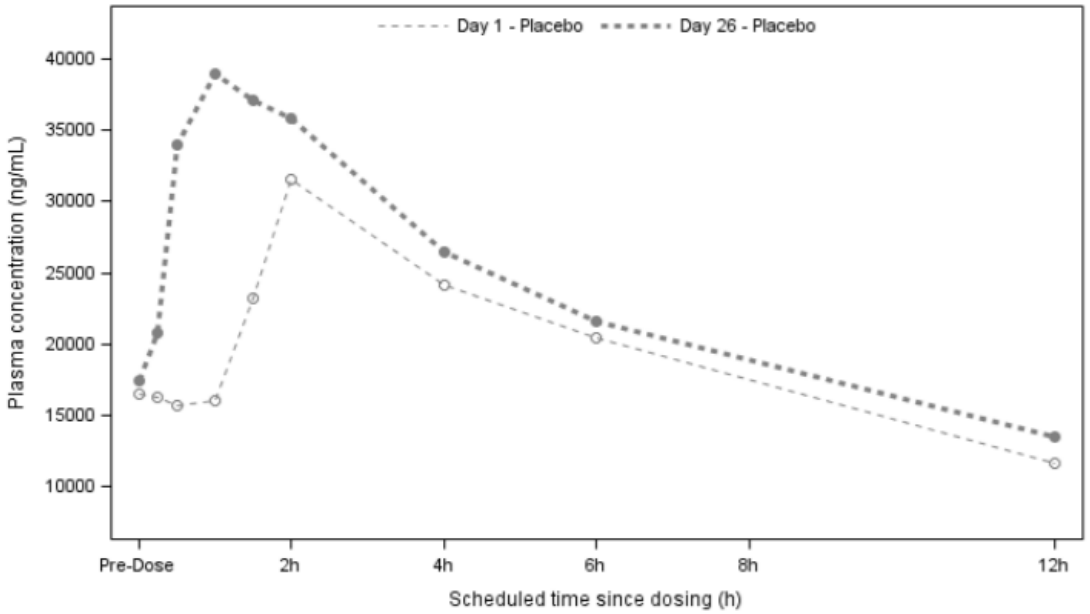
CHMP comments

It should be noticed that Epidyolex (CBD) is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam (CLB). Results from the present study illustrated how the plasma concentrations of the CLB metabolite, N-CLB were significantly higher when CLB was co-administered with CBD.

Levetiracetam Plasma Concentrations

On Day 26, plasma concentrations of LEV were higher than on Day 1 at the early time points. After 2 hours, the plasma concentration profiles were generally similar between Day 1 and Day 26, illustrated in Fig. 8.4.2.3.3.3-1, below.

Figure 8.4.2.3.3.3-1 Geometric Mean Plasma LEV Concentration Versus Time at Day 1 and Day 26 (STP Arm) (PK Population)



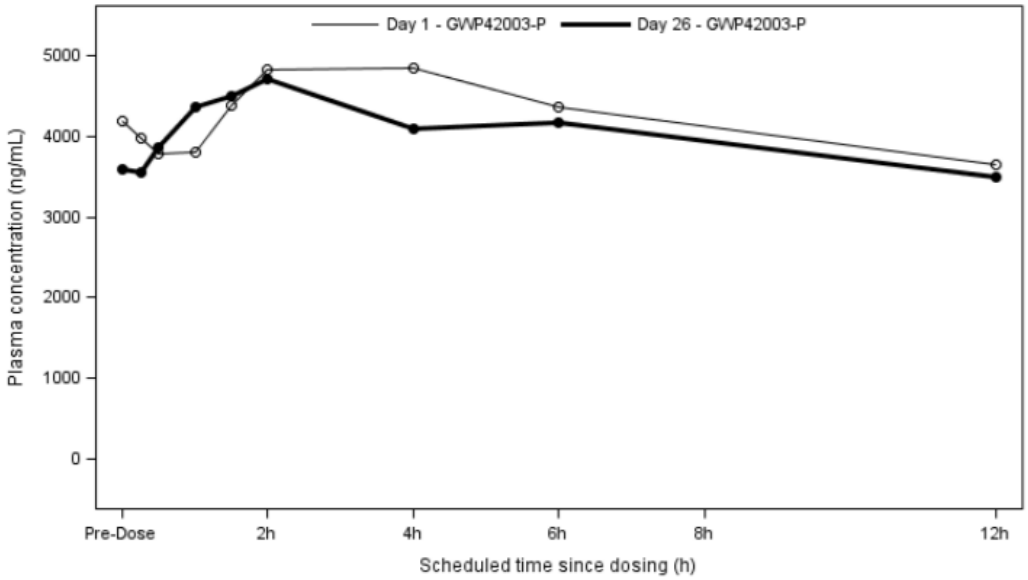
Day 1: Placebo, N=1; GWP42003-P, N=0.
Day 26: Placebo, N=1; GWP42003-P, N=0.

[redacted]

Topiramate Plasma Concentrations

On Day 26, plasma concentrations of TPM in the presence of GWP42003-P were generally similar to concentrations on Day 1 (without GWP42003-P), illustrated in Figure 8.4.2.2.3.4-1 below.

Figure 8.4.2.3.3.4-1 Geometric Mean Plasma TPM Concentration Versus Time at Day 1 and Day 26 (STP Arm) (PK Population)



Day 1: Placebo, N=0; GWP42003-P, N=2.
Day 26: Placebo, N=0; GWP42003-P, N=2.

[redacted]

Pharmacokinetic Profile – VPA Arm

Geometric mean PK parameters for VPA and 4-ene-VPA are summarized in Table 8.4.2.5.2.1-1.

Table 8.4.2.5.2.1-1 PK Parameters for VPA and Metabolite (VPA Arm) (PK Population)					
Analyte PK Parameter	Visit Day	Placebo		GWP42003-P	
		n	Geometric mean (CV%)	n	Geometric mean (CV%)
VPA					
t_{max} (h)[a]	1	3	3.92 (1.50, 4.00)	12	3.03 (0.00, 6.17)
	26	3	4.00 (0.00, 6.00)	10	1.76 (0.00, 12.00)
DN C_{max} (ng/mL/mg)	1	3	161 (54.1)	12	173 (54.7)
	26	3	168 (46.6)	10	143 (60.6)
DN AUC_{tau} (ng·h/mL/mg)	1	3	1620 (63.2)	12	1710 (64.3)
	26	3	1540 (51.4)	10	1350 (62.2)
4-ene-VPA					
t_{max} (h)[a]	1	3	5.92 (4.00, 6.00)	12	6.00 (0.25, 12.48)
	26	3	3.85 (0.00, 6.00)	10	1.73 (0.00, 11.50)
DN C_{max} (ng/mL/mg)	1	3	0.226 (39.0)	12	0.253 (102.7)
	26	3	0.19 (45.0)	10	0.182 (89.5)
DN AUC_{tau} (ng·h/mL/mg)	1	3	2.35 (42.3)	12	2.54 (104.8)
	26	3	1.86 (42.2)	10	1.7 (103.3)
4-ene-VPA/VPA ratio					
DN C_{max} (ng/mL/mg)	1	3	0.0014 (27.9)	12	0.00146 (57.0)
	26	3	0.00113 (14.2)	10	0.00128 (42.3)
DN AUC_{tau} (ng·h/mL/mg)	1	3	0.00145 (30.7)	12	0.00149 (53.2)
	26	3	0.0012 (8.7)	10	0.00126 (44.2)

[a] Median (min, max).

[redacted]

On Day 26, CBD DN Cmax was 25.4 ng/mL/(mg/kg) (CV%: 54.1) and DN AUCtau was 145 ng·h/mL/(mg/kg) (CV%: 52.3). These parameters were consistent with previous trials (Table 8.4.2.5.2.2-1).

Table 8.4.2.5.2.2-1 PK Parameters for CBD on Day 26 (VPA Arm) (PK Population)			
PK Parameter	Visit Day	GWP42003-P	
		n	Geometric mean (CV%)
t_{max} (h)[a]	26	10	2.33 (1.00, 6.00)
DN C_{max} (ng/mL/[mg/kg])	26	10	25.4 (54.1)
DN AUC_{tau} (ng·h/mL/[mg/kg])	26	10	145 (52.3)

[a] Median (min, max).

[redacted]

Geometric mean DN PK parameters for CLB and N-CLB are summarized in Table 8.4.2.5.2.3-1. There were no Day 26 data for TPM and no data available for LEV.

Table 8.4.2.5.2.3-1 PK Parameters for Other AEDs (VPA Arm) (PK Population)					
Analyte PK Parameter	**Visit Day**	**Placebo**		**GWP42003-P**	
		n	**Geometric mean (CV%)**	**n**	**Geometric mean (CV%)**
CLB					
t_{max} (h)[a]	1	0	-	3	2.33 (1.00, 4.00)
	26	0	-	3	1.00 (0.92, 4.00)
DN C_{max} (ng/mL/mg)	1	0	-	3	25.9 (53.5)
	26	0	-	3	28.2 (44.3)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	3	219 (61.3)
	26	0	-	3	277 (47.7)
N-CLB					
t_{max} (h)[a]	1	0	-	3	1.50 (0.00, 4.00)
	26	0	-	3	4.00 (0.00, 6.00)
DN C_{max} (ng/mL/mg)	1	0	-	3	71.6 (76.4)
	26	0	-	3	292 (57.0)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	3	744 (65.0)
	26	0	-	3	3200 (49.9)
N-CLB/CLB ratio					
DN C_{max} (ng/mL/mg)	1	0	-	3	2.76 (80.0)
	26	0	-	3	10.4 (11.1)
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	3	3.4 (104.8)
	26	0	-	3	11.6 (15.6)

Table 8.4.2.5.2.3-1 PK Parameters for Other AEDs (VPA Arm) (PK Population)					
Analyte PK Parameter	**Visit Day**	**Placebo**		**GWP42003-P**	
		n	**Geometric mean (CV%)**	**n**	**Geometric mean (CV%)**
TPM					
t_{max} (h)[a]	1	0	-	1	1.50 (1.50, 1.50)
DN C_{max} (ng/mL/mg)	1	0	-	1	87.7
DN AUC_{tau} (ng·h/mL/mg)	1	0	-	1	738

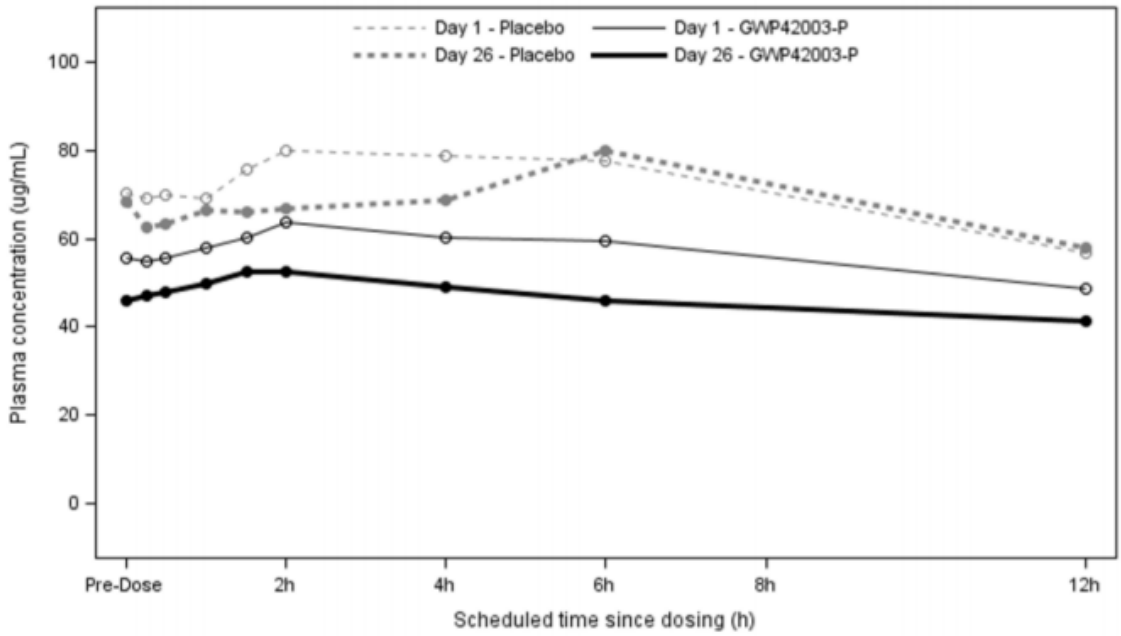
[a] Median (min, max).

[redacted]

VPA Plasma Concentrations

At all time points on Day 26, in the presence of GWP42003-P, plasma concentrations of VPA were lower than on Day 1 (without GWP42003-P). By contrast, there was no clear difference between the VPA plasma concentration vs. time curves between placebo samples on Day 26 compared with Day 1, as illustrated in Figure 8.4.2.4.1-1 below.

Figure 8.4.2.4.1-1 Geometric Mean Plasma VPA Concentration Versus Time on Day 1 and Day 26 (VPA Arm) (PK Population)



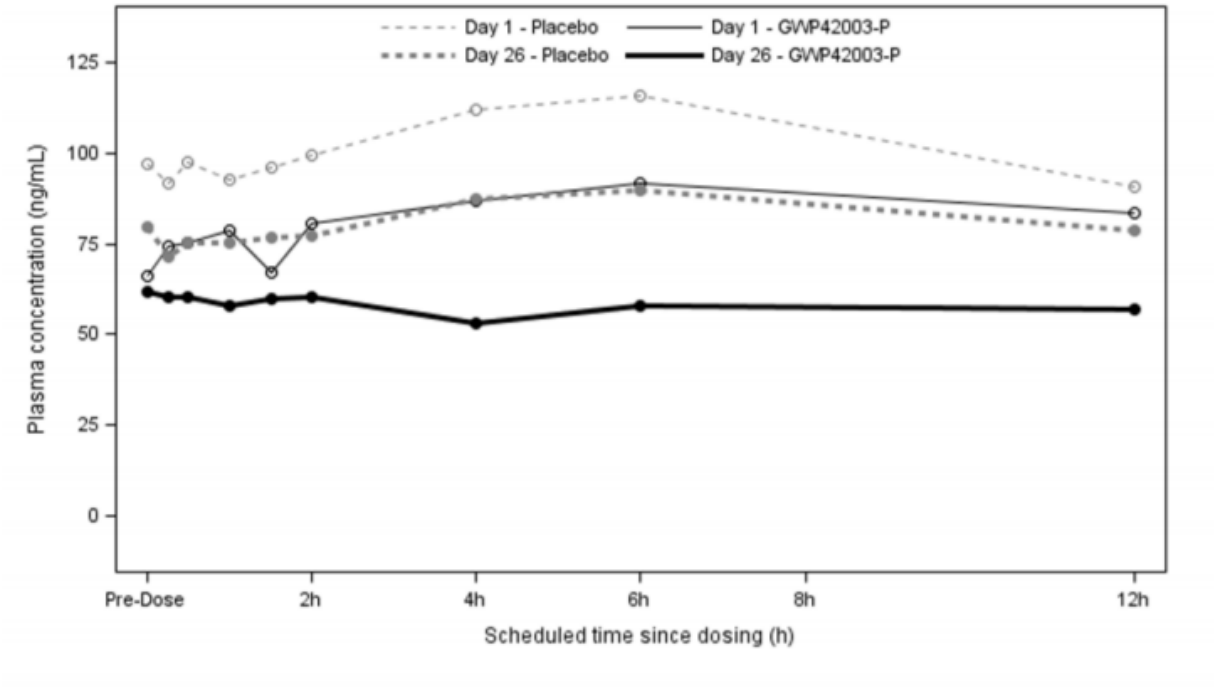
Day 1: Placebo, N=3; GWP42003-P, N=12.
Day 26: Placebo, N=3; GWP42003-P, N=10.

[redacted]

4-ene-VPA Plasma Concentrations

At all time points on Day 26, plasma concentrations of 4-ene-VPA in the presence of GWP42003-P or placebo were lower than on Day 1 (without GWP42003-P or placebo).

Figure 8.4.2.4.2-1 Geometric Mean Plasma 4-ene-VPA Concentration Versus Time on Day 1 and Day 26 (VPA Arm) (PK Population)



Day 1: Placebo, N=3; GWP42003-P, N=12.
Day 26: Placebo, N=3; GWP42003-P, N=10.

[redacted]

CHMP comments

Plasma concentrations of VPN and 4-ene-VPN were in general lower when VPN was co-administered with CBD. CBD may have some induction potential on UGT isoforms, but the clinical relevance in expected to be minor.

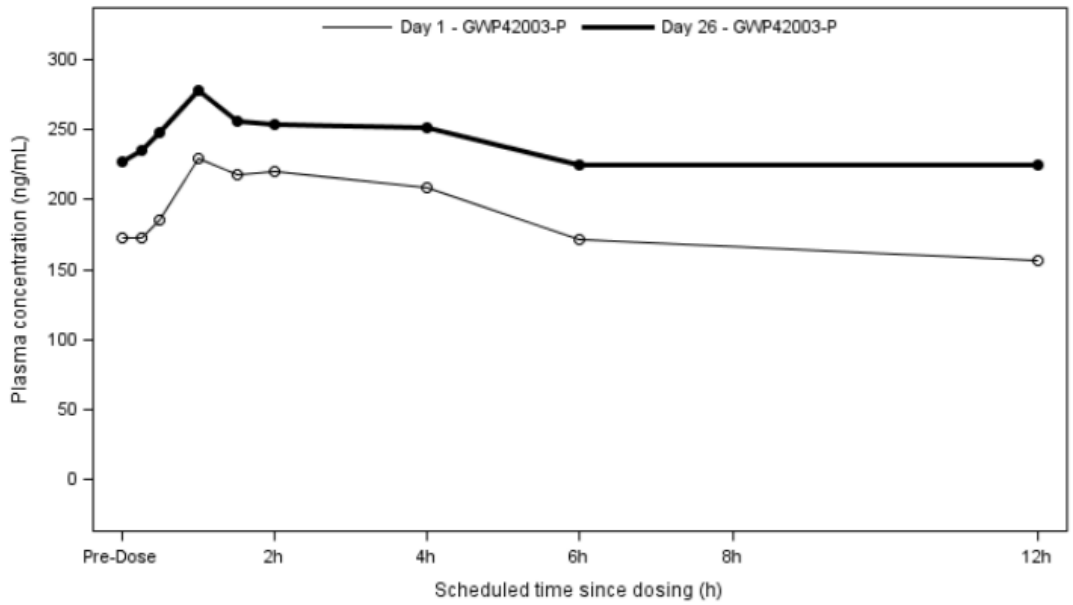
CBD Plasma Concentrations

The steady-state profile of CBD in the presence of VPA and other AEDs at Day 26 is consistent with previous trials.

Clobazam

At all time points on Day 26, plasma concentrations of CLB in the presence of GWP42003-P were higher than on Day 1 (without GWP42003-P), illustrated in fig. 8.4.2.4.4.1-1, below. Furthermore, at all time points on Day 26, plasma concentrations of N-CLB in the presence of GWP42003-P were higher than on Day 1, illustrated in Figure 8.4.2.4.4.1-2, below.

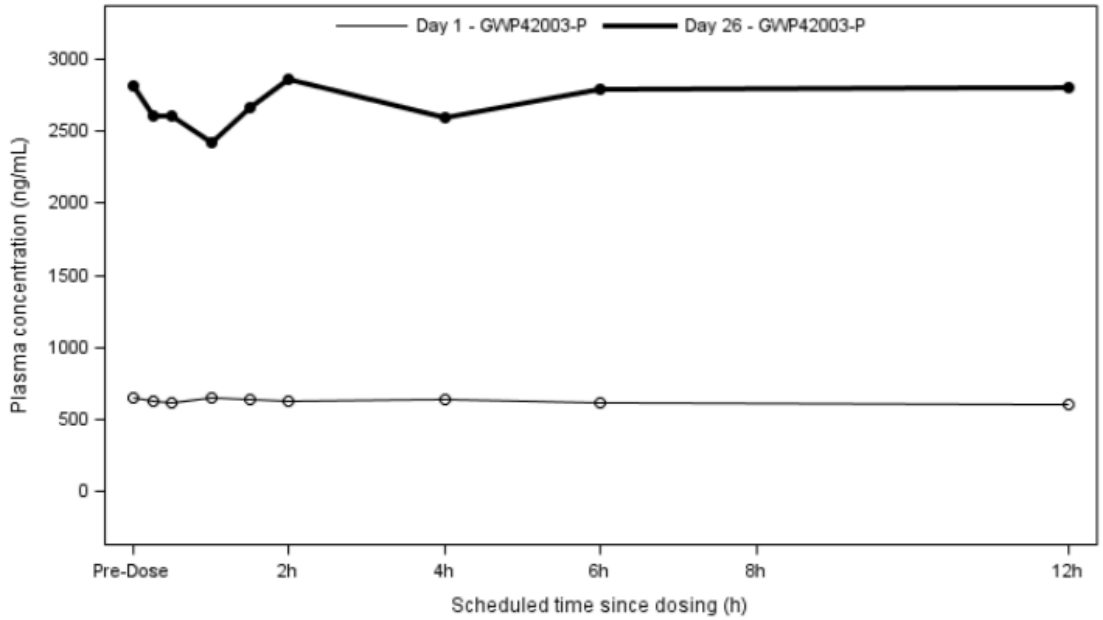
Figure 8.4.2.4.4.1-1 Geometric Mean Plasma CLB Concentration Versus Time at Day 1 and Day 26 (VPA Arm) (PK Population)



Day 1: GWP42003-P, N=4.
Day 26: GWP42003-P, N=3.

[redacted]

Figure 8.4.2.4.4.1-2 Geometric Mean Plasma N-CLB Concentration Versus Time at Day 1 and Day 26 (VPA Arm) (PK Population)



Day 1: GWP42003-P, N=4.
Day 26: GWP42003-P, N=3.

[redacted]

CHMP comments

Plasma CLB and the metabolite N-CLB were both significantly increased when administered with CBD in the VPN arm. The MAH should elaborate on and discuss the reason why P-CLB was increased in the VPN-arm but not in the STP-arm when CLB was co-administered with CBD. The objective of the study was not to investigate the interaction between CBD and CLB including the effect on N-CLB exposure and the findings reflect very few patients.

Pharmacokinetic conclusions

The MAH draws the following conclusion on the results presented:

• The PK profile of CBD after concomitant administration of STP or VPA was consistent with previous trials.

• Coadministration of GWP42003-P with STP between Days 2 to 26 did not show a marked effect of GWP42003-P on the PK of STP. There were small increases in exposure (30% for AUCtau) to STP.

• Coadministration of GWP42003-P with VPA between Days 2 to 26 did not show a marked effect of GWP42003-P on the PK of VPA or its metabolite, 4-ene-VPA. There were minor decreases in plasma Cmax and AUCtau of VPA (approximately 17% and 21%, respectively) and 4-ene-VPA (approximately 28% and 33%, respectively).

• GWP42003-P coadministration with STP or VPA showed no effect on the PK of CLB.

CHMP comments

As stated by the Applicant in the responses to the list of question, it should be noted that the study was not designed to examine the effects of CBD on PK of CLB and N-CLB. Therefore, the final bullet point in the conclusion is not supported.

2.2.3 Efficacy results

Efficacy assessments were not measured as outcomes for this trial. However, the numbers and types of seizures were collected each day from screening (Visit 1) in the DB period.

CHMP comments

Efficacy assessments were not measured as outcomes for this trial, and has not been evaluated by the MAH. Therefore, no assessment of efficacy will be included in the present AR.

2.2.4 Safety Results:

GWP42003-P administered at a dose of 20 mg/kg/day was generally well tolerated when coadministered with STP or VPA to adult patients with epilepsy. The most common TEAEs were gastrointestinal disorders (diarrhoea, nausea, and vomiting), consistent with the safety profile of GWP42003-P at this dose. Most TEAEs were of mild or moderate severity. One patient in the STP arm who received GWP42003-P experienced a severe, serious TEAE of rash, which led to discontinuation of the IMP (GWP42003-P). This was the only SAE reported in the STP arm. One patient in the VPA arm experienced a serious TEAE of moderate hypertransaminasaemia (alanine aminotransferase [ALT] 5.5 × upper limit of normal [ULN]), which led to discontinuation of the IMP (GWP42003-P). Both SAEs resolved, and the patients recovered. Both STP and VPA arms showed mean increases from baseline in ALT and aspartate aminotransferase (AST) in patients treated with GWP42003-P. There were no instances of laboratory findings that met Hy's Law criteria for potential drug-induced liver injury. Two patients receiving GWP42003-P in the STP arm had TEAEs of ALT increased and AST increased. The ALT values for 1 of these patients met the predefined toxicity criteria (≥ 2.6 × ULN) but did not exceed 3 × ULN. The ALT and AST increases for the second patient did not meet the predefined toxicity criteria. One patient (GWP42003-P) in the VPA arm had TEAEs (ALT increased, hypertransaminasaemia). A second patient (GWP42003-P) in the VPA arm had an ALT level of 365 U/L (12.2 × ULN) and an AST level of 205 U/L (5.4 × ULN) at Visit 4 (Day 28); these findings were not reported as TEAEs. There was little or no effect of GWP42003-P on other laboratory parameters, vital signs, physical examination findings, or ECGs in either STP or VPA arm. No patients had treatment-emergent suicidal ideation or behaviour. There was no evidence of abuse liability. Among the 10 patients in the STP arm who had data available, 5 (50.0%) patients in the GWP42003-P group showed a decrease in seizure frequency from baseline; seizure data were not available for 2 patients in the placebo group. Among the 16 patients in the VPA arm overall who had data available, 5 (41.7%) patients in the GWP42003-P group showed a decrease in seizure frequency from baseline compared with 2 (50%) patients in the placebo group. These results should be interpreted with caution in light of the small sample size.

CHMP comments

The most common TEAEs were gastrointestinal disorders (diarrhoea, nausea, and vomiting), consistent with the safety profile of GWP42003-P at this dose, previously reported. Most TEAEs were of mild or moderate severity. One patient in the STP arm who received GWP42003-P experienced a severe, serious TEAE of rash, which led to discontinuation of the IMP (GWP42003-P). This was the only SAE reported in the STP arm. One patient in the VPA arm experienced a serious TEAE of moderate hypertransaminasaemia (alanine aminotransferase [ALT] 5.5 × upper limit of normal [ULN]), which led to discontinuation of the IMP (GWP42003-P). Both SAEs resolved, and the patients recovered.

3. Scientific discussion

Two phase II studies (double blind phase and open-label extension) have been submitted in accordance with Article 46 of Regulation 1901/2006 as subjects < 18 years of age have been included. However, the minimum age of included subjects is 17.4 years and therefore the significance of the study from a paediatric point of view is limited.
The studies presented by the MAH have been conducted to determine whether GWP42003-P affects the pharmacokinetic (PK) profile of stiripentol (STP) or valproate (VPA). And secondary: i) To assess the safety and tolerability of GWP42003-P in the presence of STP or VPA. ii) To assess whether GWP42003-P affects the PK profile of: 2 propyl-4-pentenoic acid (4-ene-VPA), Clobazam (CLB), N-desmethylclobazam (N-CLB), Levetiracetam (LEV), Topiramate (TPM) in patients also being treated with STP or VPA and other antiepileptic drugs (AEDs).

A randomized, DB design and a placebo concurrent control was used as recommended by the European Medicines Agency (EMA) Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders, which is endorsed. The medicinal product was not administered under prespecified fed conditions**.**

The MAH has clearly presented the primary and secondary endpoint of each part of the study. All the chosen endpoints are considered relevant or the corresponding objectives. A total of 34 patients (14 patients in the STP and 20 patients in the VPA arm) were planned for randomization. A power calculation has not been presented, but the sample size appears adequate for purpose.

Demographic data has been presented adequately. The groups appear to be comparable except in regards of sex. The study has been performed in patients between 16 and 55 years of age. It is considered acceptable to extrapolate other age groups except very young children < 1 year. **(OC).**

CBD is subject to hepatic metabolism by the CYP450 isoenzyme system (mainly CYP2C19 and CYP3A4), resulting in numerous hydroxylated metabolites and an acid metabolite. CBD is also a relatively potent reversible inhibitor of the major hepatic CYP450 enzymes (CYP3A4, 2B6, 2C8, 2C9 and 2C19) in vitro23. Existing AEDs are metabolized by CYP450 enzymes, and therefore assessment of the pharmacological interaction between CBD, its metabolites and concomitant AEDs is important. The presented study assessed the potential for DDIs between CBD at steady state and STP or VPA when administered against a background of additional AEDs. STP plasma concentrations increased significantly when co-administered with CBD, confirming a pharmacokinetic D-D interaction. It should be noticed that Epidyolex (CBD) is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam (CLB). Results from the present study illustrated how the plasma concentrations of CLB (in the VPN arm) and the metabolite, N-CLB (in both the STP and VPN arm) were significantly higher when CLB was co-administered with CBD. Plasma concentrations of VPN and 4-ene-VPN were in general lower when VPN was co-administered with CBD. No new clinical findings are considered relevant to be reflected in the SmPC**.**

Safety data are presented as patient narratives for Serious Treatment-emergent Adverse Events and Other Significant Events. The most common TEAEs were gastrointestinal disorders (diarrhoea, nausea,

and vomiting), consistent with the safety profile of GWP42003-P at this dose, previously reported. One patient in the VPA arm experienced a serious TEAE of moderate hypertransaminasaemia (alanine aminotransferase [ALT] 5.5 × upper limit of normal [ULN]).

4. First List of questions

4.1. Major objections

No Major objections have been identified.

4.2. Other concerns

1. A total of 34 patients (14 patients in the STP and 20 patients in the VPA arm) were planned for randomization. However, no power calculation is presented. The MAH should therefore clarify and justify how the planned number of 34 patients was achieved, and justify that the study is powered adequately.
2. The MAH should clarify whether the medicinal product was administered under fed- or fasting conditions in that food intake is known to significantly affect the exposure of CBD, and thus may bias the results of the present interaction study/ies**.**
3. The MAH should justify that the sex of patient does not affect the PK of CBD. Furthermore, is should appear from the SmPC that the presented interaction study has only been performed in patients between 16 and 55 years of age, and that due to the complex metabolism of CBD it is difficult to extrapolate the results to other age groups, and in specific very young children.
4. STP plasma concentrations increased significantly when co-administered with CBD, confirming a pharmacokinetic D-D interaction. Therefore, close monitoring of the patient should be performed when the two drugs are administered simultaneously, herein monitoring of plasma concentrations of CBD and STP. This information should be clearly displayed in the SmPC.
5. Results from the STP-arm illustrated how the plasma concentrations of the CLB metabolite, N-CLB were significantly higher when CLB was co-administered with CBD. Therefore, closely monitoring of the patients and monitoring CLB and nCLB levels is necessary for clinical care of patients. This information should be clearly displayed in the SmPC.
6. Plasma concentrations of VPN and 4-ene-VPN were in general lower when VPN was co-administered with CBD. The MAH should elaborate on the proposed mechanism underlying this (e.g. if this is CYP- or UGT- mediated) and on the clinical importance of this result, herein a discussion of whether the efficacy of VPN may be diluted.
7. Plasma CLB and the metabolite N-CLB were both significantly increased when administered with CBD in the VPN arm. The MAH should elaborate on this result and discuss the reason why P-CLB was increased in the VPN-arm but not in the STP-arm when CLB was co-administered with CBD. Herein, the MAH should discuss the possible clinical importance of the findings.

8. In general, PKPD modelling including test of co-variates an exposure-safety analysis would add valuable information to the study. The MAH should thoroughly consider to add this information to the planned variation to support the proposed amendment of the SmPC.

Responses *Request for supplementary information in terms of Post-Authorisation Measure Application P46 005 and 006*

Question 1:

A total of 34 patients (14 patients in the STP and 20 patients in the VPA arm) were planned for randomization. However, no power calculation is presented. The MAH should therefore clarify and justify how the planned number of 34 patients was achieved and justify that the study is powered adequately.

Response to Question 1

Due to this study being a Phase II DDI study and having no efficacy components, there was no formal sample size calculation and thus no power requirements.

However, for this study the key PK endpoints (effects of CBD on VPA and STP exposure) were adequately addressed by the sample size to accurately assess the impact of CBD on plasma exposure of STP and VPA. For example, even very modest effects identified (e.g. decrease in VPA AUC_{tau} by 16%) are demonstrated to be statistically significant.

Assessment of Applicant's response

The Applicant has not provided any clarification for the planned number of 34 patients. It is acknowledged that the statistical significance of findings may be less relevant than the clinical interpretations of the findings. The study is expected to be adequate in sample size for a clinical conclusion.

Conclusion

Issue not pursued further.

Question 2:

The MAH should clarify whether the medicinal product was administered under fed- or fasting conditions in that food intake is known to significantly affect the exposure of CBD, and thus may bias the results of the present interaction study/ies**.**

Response to Question 2

Patients were instructed to be consistent in the timing of their food intake relative to dosing throughout the double-blind period; however, the exact timing of dosing in relation to meals was not recorded. The MAH believes that most patients are likely to have taken their CBD doses close to mealtimes (thus

predominantly dosed in the fed state) given the twice-daily dosing schedule necessitates administration close to breakfast and evening meals, and also the requirement to administer some concomitant AEDs with food (morning and evening). STP is instructed to be taken with food (SmPC) and the VPA SmPC also suggests taking with food may be useful in managing adverse events. The food effect studies (GWEP1544 and GWEP17076) provide evidence that the effect of food is consistent across dose and is only modestly affected by the meal composition. Furthermore, timing of meal relative to dosing (e.g. 30 min prior to dosing and immediately after dosing) also appear to have a similar and substantial impact on exposure (GWEP17076).

The exposure of CBD observed in this study are consistent with dosing being largely close to mealtimes (Figure 1) if we compare to trough levels from Phase 1 studies where dosing with food was fully documented (e.g. GWEP17028; Table 1).

Figure 1 **Geometric Mean Plasma CBD Concentration Versus Time at Steady State (Day 26) (STP Arm) (PK Population) (study** GWEP1447)

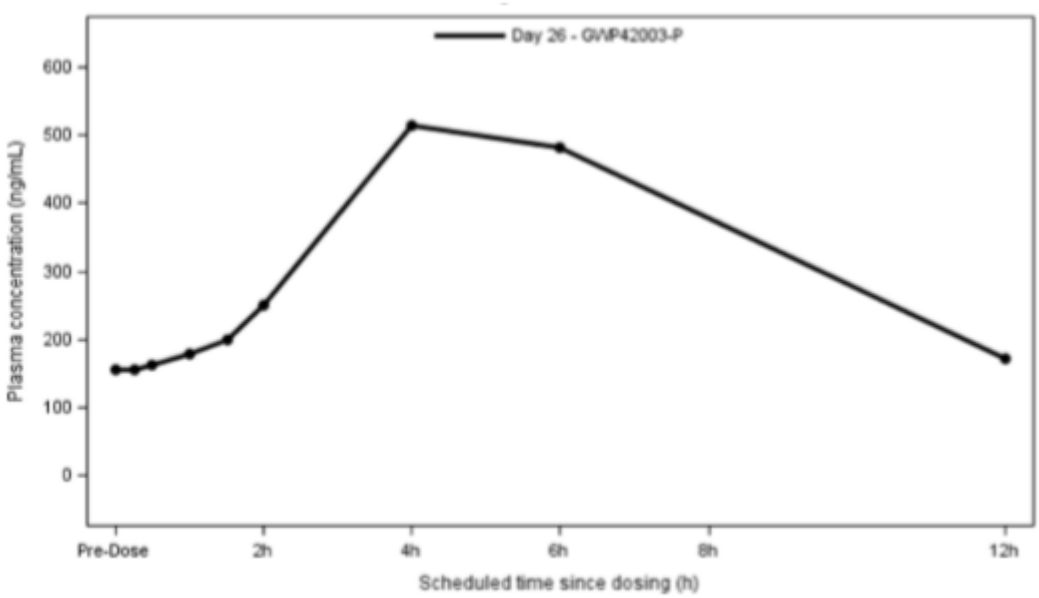


Table 1 **Summary of Steady-state Plasma CBD Trough Concentrations (ng/mL) after Administration with Food – GWEP17028.**

Trial Population: Pharmacokinetic
Analyte: CBD
Treatment: 750 mg GWP42003-P b.i.d.

Statistics	Day 22, Predose (AM)	Day 24, Predose (AM)	Day 25, Predose (AM)
Geometric mean	100	95.2	140

As the GWEP1447 study was performed in epilepsy patients, it is not possible to control all extrinsic factors and, furthermore, intrinsic factors tend to be quite heterogenous, thus, this study reflects realistic clinical outcomes. However, a definitive healthy-volunteer study was conducted to explore the effects of CBD on STP and VPA in the absence of any confounding extrinsic factors which resulted in very similar outcomes. Such definitive studies tend to be more sensitive as they are highly controlled and have more homogenous subjects. The basic conclusions of the healthy-volunteer study (GWEP1543) are the same for both STP and VPA (a small elevation in STP levels suggesting a minor interaction and little or no effect on VPA levels). It is a key part of the GWEP1543 study that subjects received CBD-OS doses shortly following a meal, and so this study can be confirmed as conducted under fully fed conditions. The concordance across the healthy-volunteer study with the patient study help validate the conclusions on interactions in patients.

Assessment of Applicant's response

The exact timing in relation to food intake was not recorded, but the Applicant states that administration is expected to be in some relation to a meal as it was to be taken in the morning and in

the evening. While this may be in line with reality it cannot be confirmed. However, exposure of CBD is overall consistent with exposure previously seen when administered with food.

Conclusion

Issue resolved

Question 3:

The MAH should justify that the sex of patient does not affect the PK of CBD. Furthermore, is should appear from the SmPC that the presented interaction study has only been performed in patients between 16 and 55 years of age, and that due to the complex metabolism of CBD it is difficult to extrapolate the results to other age groups, and in specific very young children.

Response to Question 3

There have been extensive investigations into the effect of sex on exposure during population PK analyses (GWPP16110, GWPP17003, GWPP17004, GWPP18097, GWPP19217). The outcome has been unequivocal and there is no evidence for an effect of sex on exposure to CBD or metabolites. Furthermore, there are no obvious reasons why a difference in exposure should be expected based on the known routes of clearance. In fact, the complex metabolic profile of CBD with many mechanisms being involved appears to provide exposures that are particularly robust across a wide range of demographic factors, suggesting various clearance mechanisms can compensate should one route be compromised in any individual. Indeed, this may also account for the lack of notable effects on CBD exposure by potent enzyme inhibitors (GWEP17075). Thus, there appears to be no significant effect of age, body size, metabolic phenotypes, BMI, body composition, renal function etc which suggests that in terms of exposure to CBD and DDIs affecting CBD might be expected to be similar across all age groups. Evidence from PK analysis in mainly patients (DS, LGS) do not contradict the data obtained in dedicated DDI studies. For one example, please see response to Q5 which discusses the complex 3-way interaction between CLB, STP and CBD in DS patients which is aligned with the very limited data from this study (GWEP1447) where all 3 drugs are dosed together. Furthermore, DDIs mediated through liver enzymes inhibition can be extrapolated across certain age categories as the maturation of liver enzymes from the age of 1 year is generally considered essentially equivalent to that of adults. However, extrapolation to < 1year of age (CBD is currently not indicated for this age group in the SmPC) is less predictable and usually requires physiologically-based PK modelling and paediatric PK studies to be able to assess safe and effective dosing in these populations and understand the DDI liabilities with concomitant medications.

In addition, it is typical practice to perform formal DDI studies in healthy adult volunteers as a surrogate for patients for the majority of scenarios. Some exceptions include cytotoxic agents, where there may be some risk to volunteers. It is often very challenging to perform DDI studies in patients due to the potential confounding effects of concomitant medications, comorbidities etc and in addition the variability is generally much greater in patients as they tend to be more heterogenous that subjects in a healthy-volunteer study, which can mask any DDIs. Thus, DDIs in healthy volunteers tend to be more sensitive. DDI studies for CBD with STP and VPA were already performed in healthy

adults (GWEP1543). In general, the data are well aligned between the studies in healthy volunteers and patients; that is, no substantial effect of CBD on VPA exposure and a small elevation in STP exposure were observed. The absolute values are slightly different but the magnitude of effect in general terms (weak, moderate or strong effects) are the same. Thus, taken together, no updates to the SmPC in terms of limitation of the DDI study outcome are considered applicable.

Assessment of Applicant's response

Sex has not been identified as a significant covariate for CBD PK.

The metabolism of CBD is complex and several clearance mechanisms have been identified. This is further supported by the modest effect on CBD exposure when coadministered with potent inhibitors. The DDI study has been conducted in patients 16 to 55 years of age. It is agreed that DDI studies in healthy adult volunteers are considered sensitive and also relevant for the paediatric population > 1 year of age where maturation of liver enzymes is approaching adult values. Therefore, the outcomes of study GWEP1447 are relevant for young children and elderly.

Conclusion

Issue resolved.

Question 4:

STP plasma concentrations increased significantly when coadministered with CBD, confirming a pharmacokinetic D-D interaction. Therefore, close monitoring of the patient should be performed when the 2 drugs are administered simultaneously, herein monitoring of plasma concentrations of CBD and STP. This information should be clearly displayed in the SmPC.

Response to Question 4

The SmPC language with respect to the DDI between CBD and STP is proposed to be updated to include the new information from this study (proposed updates highlighted in yellow below). It is notable that the DDI observed in GWEP1447, although statistically significant, is actually a small effect and somewhat lower than that observed in the healthy-volunteer study (GWEP1543, as reflected in the current approved SmPC), thus the key messages within the SmPC remain unaltered. As discussed in responses above, healthy-volunteer studies are the best way to test most sensitively for DDIs.

The overall PK interaction has been acknowledged being weak in nature during the MAA assessment based on data from healthy volunteers. The additional data from GWEP1447 in patients demonstrates less of an increase in exposure to STP. However, the Applicant agrees that it cannot be ruled out that there may be some clinically relevant effect in certain individuals and close monitoring of ADRs should be ensured. This is reflected in the current approved SmPC wording.

Furthermore, monitoring of plasma concentrations is clearly displayed in the SmPC in terms of any concomitant AEDs in view of the complex PK of CBD as excerpted below.

Excerpt of the SmPC interaction section 4.5

Stiripentol

When cannabidiol was combined with stiripentol in a healthy volunteer trial there was an increase in stiripentol levels of 28% for maximum measured plasma concentration (C_{max}) and 55% for AUC. In patients, however, the effect was smaller, with an increase in stiripentol levels of 17% in Cmax and 30% in AUC. The clinical importance of these results, has not been studied.The patient should be closely monitored for adverse drug reactions.

Excerpt of the SmPC interaction section 4.5

Concomitant AED treatments

The pharmacokinetics of cannabidiol are complex and may cause interactions with the patient's concomitant AED treatments. **Cannabidiol and/or concomitant AED treatment should therefore be adjusted during regular medical supervision and the patient should be closely monitored for adverse drug reactions. In addition, monitoring of plasma concentrations should be considered**.

Assessment of Applicant's response

The Applicant has updated the SmPC to reflect the study results. However, a revised text is proposed to replace the wording provided by the applicant:

"When cannabidiol is given with stiripentol in healthy volunteers, stiripentol exposure increase by 28% and 55% for Cmax and AUC, respectively. In patients, however, the effect was smaller, with an increase in stiripentol levels of 17% in Cmax and 30% in AUC. Although stiripentol toxicity may rarely occur, patients should be monitored for related-adverse events.".

Close monitoring, including monitoring of plasma concentrations is adequately reflected in the SmPC.

Conclusion

Issue resolved provided the text is amended as stated above.

Question 5:

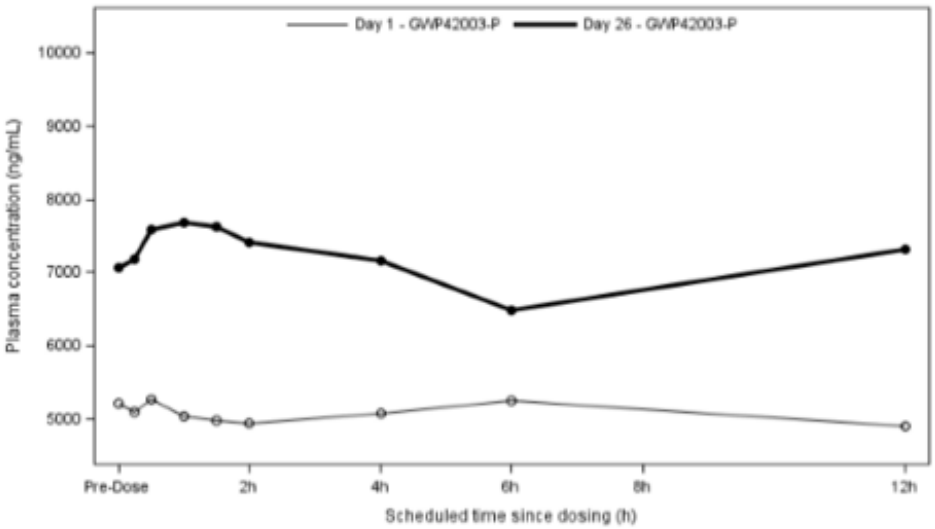
Results from the STP arm illustrated how the plasma concentrations of the CLB metabolite, N-CLB were significantly higher when CLB was coadministered with CBD. Therefore, closely monitoring of the patients and monitoring CLB and N-CLB levels is necessary for clinical care of patients. This information should be clearly displayed in the SmPC.

Response to Question 5

This study was not designed to evaluate the DDI between CBD and CLB. The DDI with CLB/N-CLB has been studied in detail elsewhere (GWEP1543, GWEP1428, GWEP17077) and suitable advice is given in SmPC when combining treatment of CBD with CLB. The information on N-CLB from GWEP1447 cannot be used to determine the magnitude or the significance of any DDI, in fact the information on CBD dosing on N-CLB in the STP arm comes from just 3 patients. In addition, the effect of CBD on N-CLB obtained from the VPA group is more marked in terms of fold change when compared with the STP arm

(see Figures below), but once again this information comes from only 3 individuals and is thus not greatly informative. The figures below (Figures 2 and 3) clearly show the impact of STP on N-CLB exposure as its baseline pre-CBD dosing (Day 1) levels are in the order of 10-fold higher in patients from the STP arm compared to those in the VPA arm. There is only a modest further elevation of N-CLB when CBD is added to the STP arm by Day 26 (approx. 1.5-fold), whereas there is a > 4-fold increase in exposure to N-CLB when CBD is added to the VPA arm. This discrepancy between the arms is due to the well-known inhibitory effects of STP on N-CLB metabolism (via CYP2C19), a mechanism believed to be partly responsible for its therapeutic effect.

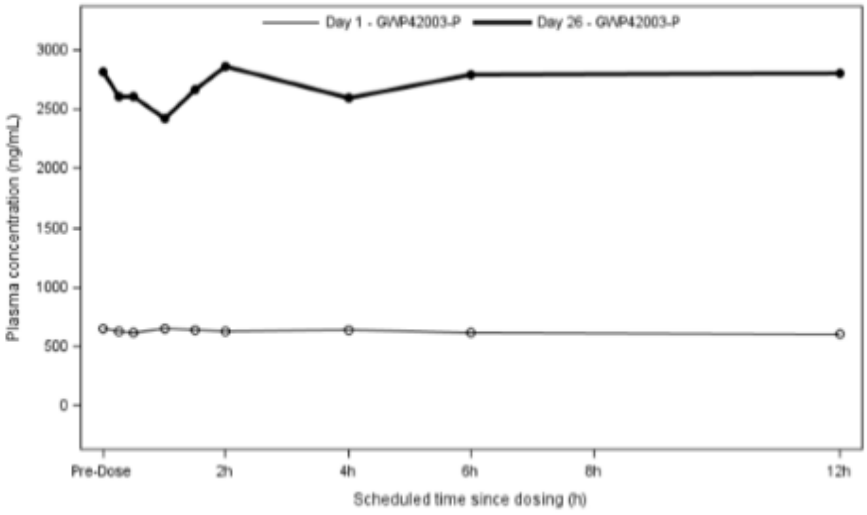
Figure 2: Geometric Mean Plasma N-CLB Concentration versus Time Without Coadministration of CBD (Day 1) and With CBD (Day 26) For STP Arm



Day 1: Placebo, N=0; GWP42003-P, N=4.
Day 26: Placebo, N=0; GWP42003-P, N=3.

[redacted]

Figure 3: Geometric Mean Plasma N-CLB Concentration versus Time Without Coadministration of CBD (Day 1) and With CBD (Day 26) For VPA Arm



Day 1: GWP42003-P, N=4.
Day 26: GWP42003-P, N=3.

[redacted]

Notwithstanding, monitoring of plasma concentrations is clearly displayed in the SmPC in terms of any concomitant AEDs as excerpted above in terms of the response to Question number 4.

Assessment of Applicant's response

It is acknowledged that even despite a significant increase in N-CLB when CLB is co-administered with either STP or VPA and CBD, then the results only reflect few patients and are inadequate for further specification of recommendations. It is recommended in the SmPC to monitor plasma concentrations when AEDs. Further monitoring of N-CLB would not be expected to provide additional information to the prescriber, where the bi-directional pharmacokinetic interactions between CBD and CLB is well described to contribute to the anticonvulsive effect.

Conclusion

Issue resolved.

Question 6:

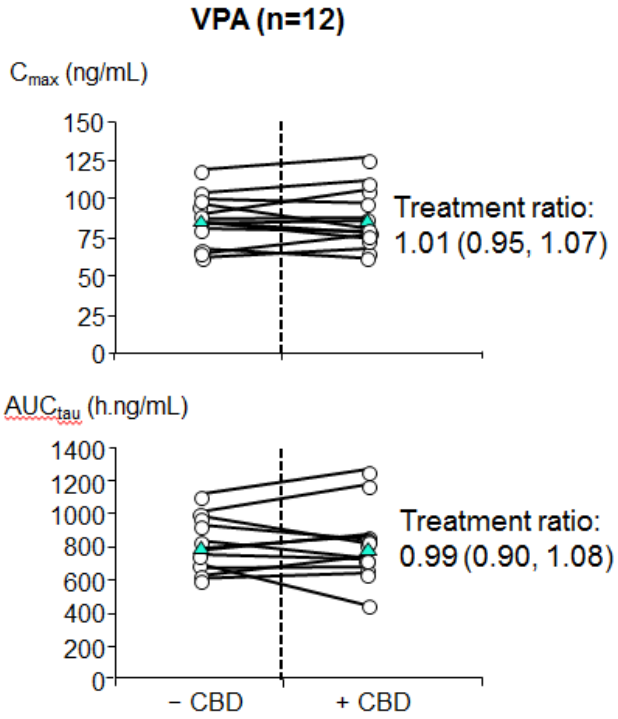
Plasma concentrations of VPN and 4-ene-VPN were in general lower when VPN was coadministered with CBD. The MAH should elaborate on the proposed mechanism underlying this (e.g. if this is CYP- or UGT- mediated) and on the clinical importance of this result, herein a discussion of whether the efficacy of VPN may be diluted.

Response to Question 6

While it is true that the levels of VPA and 4-ene-VPA appear to be a little lower on coadministration with CBD, we do not believe this is a clinically relevant effect (only ~16% for VPA AUC) and may be a chance finding. The magnitude of the impact does not reach the level recognized as representing even a weak effect in DDI studies (25 to 100 % increase in exposure). The level of the effect, even if it were a true measure of the magnitude and replicable, is very likely to be overshadowed by variability from

various other sources. In addition, the DDI between VPA and CBD was examined in a healthy-volunteer study (GWEP1543) which looked in detail at the potential interaction in both directions. This study did not show any change in VPA exposure when given with CBD (Figure 4).

Figure 4 VPA Exposures with and without CBD Coadministration (GWEP1543)



[redacted]

In vitro data indicate that CBD is capable of inhibiting both CYP2B6- and CYP2C9-mediated activity. These two CYP450 isoforms are involved in the metabolism of VPA to 4-ene-VPA, therefore, this may, in part, explain the decrease in 4-ene-VPA C_{max} and AUC_{tau} when VPA is coadministered with CBD. As 4-ene-VPA is not an active metabolite, the slightly diminished exposure to this metabolite when VPA is combined with CBD would not be expected to affect efficacy. In fact, as this metabolite is a putative hepatotoxin, reduced levels may have some beneficial effects in patients. The decrease in VPA C_{max} and AUC_{tau} is much less pronounced and, if a real effect, may be the result of CBD having the potential to induce some UGT isoforms (CBD was shown in vitro to induce some enzymes presumed to be via activation of PXR) as VPA is readily glucuronidated.

Assessment of Applicant's response

The issue has been adequately addressed by the Applicant. CBD may have some induction potential on UGT isoforms. There are no indications clinical relevance when CBD is coadministered with VPA.

Conclusion

Issue resolved.

Question 7:

Plasma CLB and the metabolite N-CLB were both significantly increased when administered with CBD in the VPA arm. The MAH should elaborate on this result and discuss the reason why N-CLB was increased in the VPA arm but not in the STP arm when CLB was coadministered with CBD. Herein, the MAH should discuss the possible clinical importance of the findings.

Response to Question 7

Firstly, it should be noted that this study was not designed to examine the effects of CBD on PK of CLB and N-CLB. This DDI has been extensively investigated in multiple studies, is well understood (GWEP1428, GWEP1543, GWEP17077) and relevant clinical guidance concerning dose adjustments and monitoring of ADRs / plasma concentrations provided in the SmPC. In GWEP1447, there were only 3 patients post-CBD in either arm who provided data for CLB and N-CLB. Thus, any definitive conclusions cannot be made on these data about significance or magnitude of effects. The apparent impact of CBD on CLB between the 2 arms cannot sensibly be compared, and the studies detailed above should be considered for an understanding of the effect of CBD on CLB levels.

Assessment of Applicant's response

The objective of the study was not to investigate the interaction between CBD and CLB including the effect on N-CLB exposure. The Applicant has not commented on the difference observed in the VPA and STP arm, but emphasises that the findings reflect very few patients. This is acknowledged.

Conclusion

Issue resolved.

Question 8:

In general, PKPD modelling including test of co-variates and exposure-safety analysis would add valuable information to the study. The MAH should thoroughly consider to add this information to the planned variation to support the proposed amendment of the SmPC.

Response to Question 8

Pooled population PK modelling has also explored safety exposure-response relationships for CBD. These have been reported elsewhere (see referenced population PK analyses in relation to Q3) and are based on the 2 pivotal LGS trials and have informed the SmPC (in section 5.2). Such exposure response for VPA and STP have not been developed but are unlikely to be of utility in the case of GWEP1447 due to the lack of clinically important changes in exposure on coadministration.

Assessment of Applicant's response

The Applicant has not planned to explore data further with PKPD modelling. This is noted.

Conclusion

Issue not pursued further.

5. Overall conclusion

The MAH has submitted a synoptic CSR and a clinical for the Study GWEP1447 (Double-blind Phase and long-term extended) in accordance with Article 46 of Regulation 1901/2006 as subjects < 18 years have been included. A variation (type II-008G) has been submitted in parallel. Minor changes to the SmPC as a result of the studies is anticipated.

☒ **PAM fulfilled (all commitments fulfilled),** provided the MAH implement the proposed alternative SmPC wording.